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Late recurrence of locally advanced cervical cancer treated with concurrent chemoradiotherapy

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ABSTRACT

Introduction. This study aimed to compare clinicopathological factors between late-recurrence and early--recurrence patients (using late recurrence at ≥ 3 years and 5 years as cut-off points) in locally advanced cervical cancer (LACC) treated with concurrent chemoradiotherapy (CCRT). This study also identified independent risk factors for late recurrence.

Material and methods. We analyzed data from LACC patients treated at Songklanagarind Hospital between 2002 and 2016, who had received definitive CCRT. A total of 1231 patients were retrospectively reviewed.

Results. The median follow-up was 4.6 years, and the total recurrence rate was 28.7% (353 of 1231 patients). The late recurrence rates were 7.4% and 2.2% for ≥ 3 and 5 years after CCRT, respectively. When comparing the risk factors of late recurrence at ≥ 3 years with early recurrence, we found that anemia and thrombocytosis were found less frequently in late recurrence (26.2% *vs*. 46.9% and 9.8% *vs*. 23.6%, respectively). At ≥ 5 years, no differences in risk factors between the recurrent groups were found. When including only patients that remained tumor-free after 3 years, stage III–IVA was the only independent risk factor associated with late recurrence at ≥ 3 years ($p = 0.042$). Univariate analysis showed no significant associated factor for late recurrence after 5 years.

Conclusions. Late recurrence at ≥ 3 years was not rare. Even though we could not find any significant association between clinicopathologic factors and late recurrence after 5 years, 2.2% of patients still had late recurrence. Long-term follow-up should be considered, especially for more advanced stages (stage III–IVA).

Key words: chemoradiotherapy, recurrence, risk factors, uterine cervical neoplasms

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Introduction

Cervical cancer is the fourth most common cancer in women worldwide [1]. The majority of cervical cancer cases are at a locally advanced stage (IB–IVA) at presentation. For about two decades, concurrent chemoradiotherapy (CCRT) has been the standard treatment for locally advanced cervical cancer (LACC) [2, 3]. Although, progression-free survival at 5 years after CCRT is 57–68% [4, 5], the (pathologic) complete response rate after CCRT ranges between 45.7% and 55% [6–8]. However, 26–30.1% of these patients experience disease recurrence [4, 9].

In general, the median time to recurrence of cervical cancer in both early and locally advanced stages ranges from 9 to 21.8 months after initial treatment [10–15]. Therefore, surveillance guidelines usually recommend following the patient closely in the first 2 years and then less closely for up to 5 years [16–18]. However, opinions on the optimal follow-up period

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after 5 years and which patients needed long-term follow-up are still equivocal. The National Comprehensive Cancer Network (NCCN) guidelines [16] agree with the Society of Gynecologic Oncology (SGO) [17] recommendations. The frequency of their surveillance program is based on the risk of recurrence. They suggest follow-up evaluations should be performed every 3–6 months for the first 2 years, followed by every 6–12 months for the next 3 years, and then annually after 5 years. Meanwhile, the European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) guidelines recommend follow-ups every 3–4 (6) months for the first 2 years, and then 6–12 months up to 5 years, but they do not offer any recommendation on how to follow up patients after 5 years [18]. However, many studies have reported that cervical cancer patients experience late recurrence [19–24]. For early-stage cancer, the rate of recurrence at more than 3 years has been reported at 5.9%, and that of more than 5 years, had been observed at 4.8% [19]. For LACC, the recurrence rate at more than 5 years has been found to range from 2.4% to 5.1% [20–22], and that of more than 10 years has been reported at 0.76% [23]. Defining the clinicopathologic factors associated with recurrence after 3–5 years is important to determine which patients are at high risk of developing late recurrence.

Focusing on LACC, previous studies have reported that late recurrence is found more often in more advanced-stage cancers (stage II–IV more often than stage I) [20, 22–24]. Furthermore, squamous cell carcinoma is the most common histological type associated with late recurrence [20, 23, 24]. However, the mentioned LACC studies did not report any independent prognostic factors, and most of the patients involved were treated with radiation therapy alone, not CCRT [20, 22–24]. So far, only one study has investigated independent risk factors for late recurrence (more than 3 years); its study population had early-stage cervical cancer that was treated with radical surgery [19]. The authors found that pelvic lymph node metastasis and deep stromal invasion at initial diagnosis were significant factors associated with late recurrence [19]. Hence, further data concerning independent risk factors for late recurrence in LACC treated with CCRT are needed.

Therefore, in this study, we compared clinicopathological factors between patients who developed late recurrence (at more than 3 years and 5 years) and those who developed early recurrence. Furthermore, we identified independent clinicopathological factors associated with late recurrence in LACC patients treated with CCRT.

Material and methods

Patient selections and data collection

This study obtained approval from the Human Research Ethics Committee at our institution (IRB number REC 62-317-7-4). In this retrospective study, we included all patients with LACC (stage IB2-IVA; FIGO 2009) with squamous cell carcinoma, adenocarcinoma, or adenosquamous cell carcinoma histological results who received definitive CCRT with cisplatin regimens between January 2002 and January 2016 at Songklanagarind Hospital. Patients who had an incomplete treatment response after CCRT, underwent an incomplete plan of radiation treatment, or had another primary cancer were excluded. We reviewed data at initial diagnosis from patients' medical records and the Songklanagarind cancer registry database, which included age, FIGO stage, histology, and pretreatment blood work-up (hemoglobin level, white blood cell count, and platelet count). In addition, data regarding recurrence status, site of recurrence, date of recurrence, date of death, and last patient status were also retrieved from the same database. Lastly, information on the radiation techniques was retrieved from the Eclipse Radiation Planning System version 10.0.

Treatment regimen

The decision on whether the patient would receive CCRT was based on an agreement between an attending gynecologic oncologist and radiation oncologist after considering patients' preference, performance status, and relevant medical conditions. The radiation therapy consisted of external beam radiation (EBRT) and high-dose-rate intracavitary brachytherapy (HDR-ICBT). Patients were treated with either conventional two-dimensional radiotherapy (2D-RT), three-dimensional radiotherapy technique (3D-CRT), or intensity-modulated radiotherapy (IMRT) depending on the radiation oncologist's decision. Generally, the whole-pelvis EBRT field was employed using the opposing anterior-posterior fields or the four-field box. Patients who had para-aortic lymph node metastasis were treated with extended-field RT (EFRT) to cover the para-aortic lymph nodes. Briefly, a 45–50-Gy dose of whole-pelvis EBRT was delivered in 1.8–2 Gy daily fractions, 5 days per week. The parametrium and pelvic sidewall were boosted up to 54 to 60 Gy in patients who had parametrium and/or pelvic sidewall involvement. HDR-ICBT was delivered once per week at a fractional dose of 6.5–7 Gy, administered 4 times at point A. The cumulative linear quadratic equivalent doses (EQD2), prescribed at point A, were 80–90 Gy depending

on tumor size. Concurrently, cisplatin at 40 mg/m^2 was given weekly during radiation therapy. A dose reduction was considered in patients with renal dysfunction, lower performance status, and advanced age.

Surveillance methods, detection of recurrence, treatment after recurrence, and survival after treatment (SAR)

The surveillance protocol consisted of follow-up every 3 months in the first year, every 4 months in the second year, every 6 months in the third to fifth years, and then annually. A clinical history and physical examination, including a pelvic-rectal examination, was performed at every visit. A chest X-ray was taken yearly, whereas a cervicovaginal cytology study was performed optionally. Annual abdominal tomographic (CT) scans, magnetic resonance imaging (MRI) studies, or ultrasonography were not performed routinely unless clinically indicated. A diagnosis of recurrence was based on physical and pelvic examinations, imaging of suspicious lesions, and/or pathological confirmation. The sites of recurrence were categorized as local, lymphogenous, and distant metastases. The timing of recurrence was defined in relation to the time elapsed after complete treatment. The cut-off point for late recurrence in our study was divided into two periods — more than 3 years [19] and more than 5 years [19–22] after complete treatment. The treatment for disease recurrence depended on previous initial treatment, site of recurrence, and patient performance status. SAR was defined as the time from the detection of recurrence to the date of death or the last visit date.

Statistical analysis

Descriptive statistics were used for patient characteristics and summarized as percentages or medians. The comparison of clinicopathologic characteristics between early and late recurrence was performed using the Chi-square or Fisher's exact test, the unpaired t-test, or the Wilcoxon rank-sum test as appropriate. The potential risk factors for late recurrence at more than 3 years were identified using survival analysis considering the start of the risk period to be 3 years after initial treatment. A Kaplan-Meier analysis was performed to identify variables and their association with clinicopathologic factors, which could affect late recurrence, and were evaluated using the Cox regression model. In addition, SAR was compared between early and late recurrence and, then tested using the log-rank test. Statistical significance was indicated by a p-value of < 0.05. All statistical analyses were performed using the R program version 3.6.1.

Results

A total of 1339 patients were considered for inclusion. One hundred patients were excluded due to an incomplete treatment response after CCRT, and 8 patients were excluded due to undergoing an incomplete plan of radiation treatment. Therefore, 1231 patients met the inclusion criteria and were analyzed in our study (Fig. 1). The median follow-up time was 4.6 years (0.09–14.2 years). We found a total recurrence rate of 28.7% (353 of 1231 patients), and the median time to

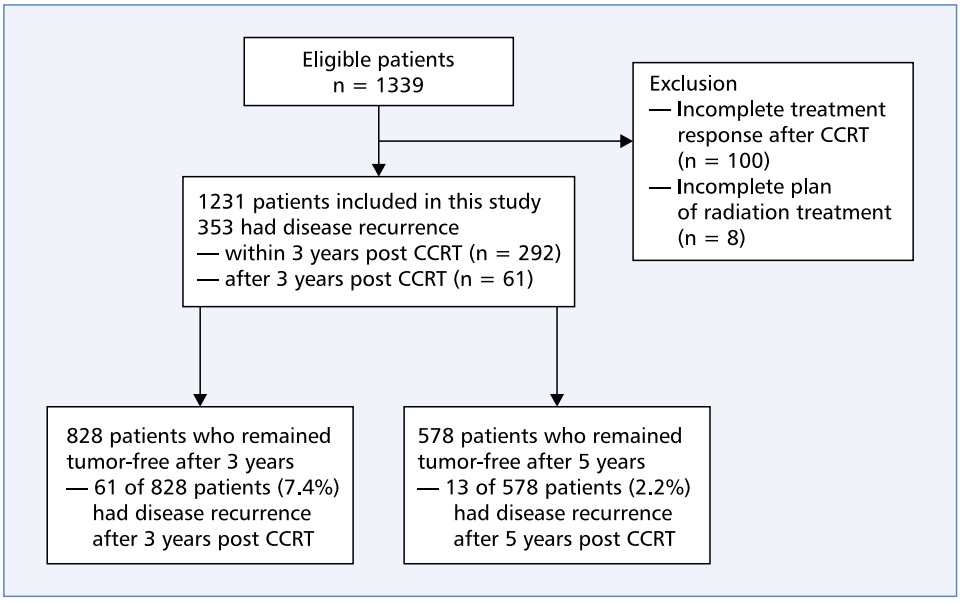

Figure 1. Flow diagram of patients included in the study; CCRT — concurrent chemoradiotherapy

Table 1. Clinicopathologic characteristics at diagnosis and clinical outcomes of patients between early and late recurrence (more than 3 years)

Variables	Total recurrence (353), n (%)	Early recurrence (292), n (%)	Late recurrence (61), n (%)	p-value[a]
Age at diagnosis (years)				
< 40	56 (15.9)	46 (15.8)	10 (16.4)	0.224
40–59	246 (69.7)	208 (71.2)	38 (62.3)	
≥ 60	51 (14.4)	38 (13)	13 (21.3)	
Stage				
IB2–IIB	188 (53.3)	149 (51.0)	39 (63.9)	0.090
III–IVA	165 (46.7)	143 (49.0)	22 (36.1)	
Histological subtypes				
SCC	248 (70.3)	203 (69.5)	45 (73.8)	0.634
AC	85 (24.1)	71 (24.3)	14 (23)	
ASC	20 (5.7)	18 (6.2)	2 (3.3)	
Hemoglobin level (g/dL)				
< 11	153 (43.3)	137 (46.9)	16 (26.2)	0.005
≥ 11	200 (56.7)	155 (53.1)	45 (73.8)	
White blood cell count (/μL)				
< 10000	247 (70)	204 (69.9)	43 (70.5)	1.000
≥ 10000	106 (30)	88 (30.1)	18 (29.5)	
Platelets counts (/μL)				
< 400000	278 (78.8)	223 (76.4)	55 (90.2)	0.026
≥ 400000	75 (21.2)	69 (23.6)	6 (9.8)	
Radiation techniques	306 (86.7)	252 (86.3)	54 (88.5)	0.797
2D-RT	47 (13.3)	40 (13.7)	7 (11.5)	
3D-CRT or IMRT				
Symptoms status at recurrence				
Yes	289 (81.9)	243 (83.2)	46 (75.4)	0.239
No	62 (17.6)	47 (16.1)	15 (24.6)	
Unknown	2 (0.6)	2 (0.7)	0 (0)	
Site of recurrence				
Inside radiation field	69 (19.5)	58 (19.9)	11 (18)	0.937
Outside radiation field	162 (45.9)	133 (45.5)	29 (47.5)	
Combined	122 (34.6)	101 (34.6)	21 (34.4)	

AC — adenocarcinoma; ASC — adenosquamous cell carcinoma; IMRT — intensity-modulated radiotherapy; SCC — squamous cell carcinoma; 2D-RT — conventional two-dimensional radiotherapy; 3D-CRT — three-dimensional radiotherapy technique; [a]P-value compares early and late recurrence

the first recurrence was 1.1 years (0.3–11.8 years). The clinicopathologic patient characteristics at diagnosis and the clinical outcomes of both early and late recurrence (more than 3 years) are shown in Table 1. Most patients were 40–59 years old at diagnosis. More than half of them had tumors of IB-IIB stages, and the most common histological subtype was squamous cell carcinoma. When comparing early and late recurrence, no differences in terms of age at diagnosis, cancer stage, histological subtype, white blood cell level, radiation technique, symptom status at recurrence, and site of recurrence were detected. Patients who had pretreatment anemia (hemoglobin level < 11 g/dL) and thrombocytosis (platelets count ≥ 400000/μL) were associated less frequently with late recurrence compared to early recurrence (26.2% *vs.* 46.9% and 9.8% *vs.* 23.6%, respectively).

Details related to the recurrence site are shown in Table 2. There was no difference concerning the site of recurrence between early and late recurrence (more than 3 years). Liver metastases tended to be less frequent in late compared to early recurrence, but this difference did not reach statistical significance (p = 0.084). Moreover, the lung was the most common organ affected by distant metastasis in both early and late recurrence.

In the analysis to identify clinicopathologic factors associated with late recurrence, we included only the patients who had remained tumor-free after 3 years post-treatment; thus, 828 patients were analyzed. A recurrence rate of 7.4% (61 patients of 828) was detected. The 1-year and 3-year probabilities of late recurrence according to patient characteristics and the multivariate analysis findings are shown in Table 3. FIGO

Table 2. Site of recurrence in early and late recurrence (more than 3 years)

Variables[a]	Total recurrence n (%), n = 353	Early recurrence n (%), n = 292	Late recurrence n (%), n = 61	p-value[b]
Local recurrence				
Limited to cervix and adjacent organ[c]	58 (16.4)	48 (16.4)	10 (16.4)	1 0.828
Beyond cervix and adjacent organ[d]	76 (21.5)	64 (21.9)	12 (19.7)	
Lymphogenous metastasis				
Paraaortic node	149 (42.2)	124 (42.5)	25 (41)	0.944
Pelvic node	95 (26.9)	81 (27.7)	14 (23)	0.543
Supraclavicular node	70 (19.8)	62 (21.2)	8 (13.1)	0.204
Inguinal node	21 (5.9)	17 (5.8)	4 (6.6)	1
Distant metastasis				
Lung	107 (30.3)	84 (28.8)	23 (37.7)	0.219
Bone	65 (18.4)	55(18.8)	10 (16.4)	0.790
Liver	51 (14.4)	47 (16.1)	4 (6.6)	0.084
Brain	6 (1.7)	6 (2.1)	0 (0)	0.559

[a]Some patients had more than 1 recurrence site; [b]P-value compares early and late recurrence; [c]Recurrence at the cervix, uterus, upper 2/3 of the vagina, and parametrium; [d]The intrapelvic region includes the pelvic side wall and lower 1/3 of the vagina, does not include the pelvic lymph node

Table 3. Kaplan-Meier analysis and multivariate analysis of the probability of late recurrence by characteristics of patients who remained tumor-free after 3 years

Variables	Probability of recurrence			Multivariate analysis		
	1-year probability of recurrence[a] (95% CI)	3-year probability of recurrence[a] (95% CI)	p-value	Hazard ratio	95% confidence interval	p-value
Overall	4.2% (3.0–5.8)	7.7% (5.9–9.9)		–	–	–
Age at diagnosis (years)						
< 40	2.8% (0.9–8.4)	9.5% (5.1–17.6)	0.614	–	–	–
40–59	3.8% (2.5–5.9)	6.8% (4.9–9.5)				
≥ 60	6.3% (3.3–11.8)	9.1% (5.2–15.6)				
Stage						
IB2–IIB	3.5% (2.3–5.4)	6.3% (4.5–8.7)	0.063	1 (reference)	–	0.042
III–IVA	6.0% (3.4–10.3)	11.5% (7.6–17.2)		1.77	1.04–3.01	
Histological subtypes						
SCC	3.9% (2.6–5.7)	6.8% (5.0–9.2)	0.271	1 (reference)	–0.89–3.03	0.200
AC	5.0% (2.4–10.3)	10.7% (6.3–17.9)		1.65	0.57–9.73	
ASC	7.7% (1.1–43.3)	16.1% (4.3–50.6)		2.35		
Hemoglobin level (g/dL)						
< 11	2.3% (1.0–5.5)	7.6% (4.5–12.5)	0.802	–	–	–
≥ 11	4.9% (3.4–7.0)	7.7% (5.7–10.4)				
White blood cell count (/μL)						
< 10000	4.4% (3.0–6.4)	7.2% (5.3–9.8)	0.265	–	–	–
≥ 10000	3.3% (1.5–7.2)	9.1% (5.6–14.7)				
Platelets counts (/μL)						
< 400000	4.5% (3.2–6.4)	7.8% (5.9–10.3)	0.369	–	–	–
≥ 400000	2.0% (0.5–7.6)	6.7% (3.0–14.4)				
Radiation techniques						
2D-RT	3.9% (2.6–5.7)	7.6% (5.8–10.0)	0.847	–	–	–
3D-CRT or IMRT	5.6% (2.7–11.5)	5.6% (2.7–11.5)				

AC — adenocarcinoma; ASC — adenosquamous cell carcinoma; CI — confidence interval; IMRT — intensity-modulated radiotherapy; SCC — squamous cell carcinoma; 2D-RT — conventional two-dimensional radiotherapy; 3D-CRT — three-dimensional radiotherapy technique; [a]Following 3 years after tumor-free post-initial concurrent chemoradiotherapy

Table 4. Clinicopathologic characteristics at diagnosis and clinical outcomes of patients between early and late recurrence (more than 5 years)

Variables	Total recurrence (353), n (%)	Early recurrence (340), n (%)	Late recurrence (13), n (%)	p-value[a]
Age at diagnosis (years)				
< 40	56 (15.9)	53 (15.6)	3 (23.1)	0.444
40–59	246 (69.7)	239 (70.3)	7 (53.8)	
≥ 60	51 (14.4)	48 (14.1)	3 (23.1)	
Stage				
IB2–IIB	188 (53.3)	180 (52.9)	8 (61.5)	0.744
III–IVA	165 (46.7)	160 (47.1)	5 (38.5)	
Histological subtypes				
SCC	248 (70.3)	238 (70)	10 (76.9)	0.652
AC	85 (24.1)	82 (24.1)	3 (23.1)	
ASC	20 (5.7)	20 (5.9)	0 (0)	
Hemoglobin level (g/dL)				
< 11	153 (43.3)	149 (43.8)	4 (30.8)	0.518
≥ 11	200 (56.7)	191 (56.2)	9 (69.2)	
White blood cell count (/μL)				
< 10000	247 (70)	237 (69.7)	10 (76.9)	0.803
≥ 10000	106 (30)	103 (30.3)	3 (23.1)	
Platelets counts (/μL)				
< 400000	278 (78.8)	266 (78.2)	12 (92.3)	0.383
≥ 400000	75 (21.2)	74 (21.8)	1 (7.7)	
Radiation techniques				
2D-RT	306 (86.7)	293 (86.2)	13 (100)	0.306
3D-CRT or IMRT	47 (13.3)	47 (13.8)	0 (0)	
Symptoms status at recurrence				
Yes	289 (81.9)	277 (81.5)	12 (92.3)	0.605
No	62 (17.6)	61 (17.9)	1 (7.7)	
Unknown	2 (0.6)	2 (0.6)	0 (0)	
Site of recurrence				
Inside radiation field	69 (19.5)	65 (19.1)	(30.8)	0.580
Outside radiation field	162 (45.9)	157 (46.2)	(38.5)	
Combined	122 (34.6)	118 (34.7)	4 (30.8)	

AC — adenocarcinoma; ASC — adenosquamous cell carcinoma; IMRT — intensity-modulated radiotherapy; SCC — squamous cell carcinoma; 2D-RT — conventional two-dimensional radiotherapy; 3D-CRT — three-dimensional radiotherapy technique; [a]P-value compares early and late recurrence

stage III–IVA tended to have a higher probability of association with late recurrence (p = 0.063), and in the multivariate analysis, a significant correlation was revealed [hazard ratio (HR) = 1.77, 95% confidence interval (CI) 1.04–3.01, p = 0.042].

Median SAR was 7.0 months (95% CI 6.24–8.2) for the early recurrence group and 11.2 months (95% CI 8.9–16.0) for the late recurrence group (p = 0.049). Meanwhile, 1-year SAR was 31.7% (95% CI, 26.7– 37.6%) for the early recurrence group and 45.9% (95% CI 33.7–62.4%) for the late recurrence group.

Furthermore, to analyze late recurrence, we included only patients who remained tumor-free after 5 years post-treatment. The total number of patients included in this analysis was 578. The recurrence rate was 2.2% (13 of 578 patients). There was no significant difference in clinicopathologic factors between the groups (Tab. 4). Moreover, the univariate analysis revealed no significant association of factors with late recurrence among these patients. The details concerning the site of recurrence in the patients who remained tumor-free after 5 years are shown in Table 5. The lung was the only distant metastasis site among patients with recurrence after 5 years; no recurrence in the liver, bones, or brain was observed. Median SAR was 7.8 months (95% CI 6.8–8.9) for the early recurrence group and 10.4 months (95% CI 8.5–no upper limit) for the late recurrence group (p = 0.7). Finally, 1-year SAR was 33.6% (95% CI 28.8–39.1%) for the early recurrence group and 46.3% (95% CI 21.8–98.2%) for the late recurrence group.

Table 5. Site of recurrence in patients who had remained tumor-free after 5 years

Variables[a]	Recurrence n (%), n = 13
Local recurrence	
Limited to cervix and adjacent organ[b]	(23.1)
Beyond cervix and adjacent organ[c]	(30.8)
Lymphogenous metastasis	
Paraaortic node	4 (30.8)
Pelvic node	3 (23.1)
Supraclavicular node	0 (0)
Inguinal node	2 (15.4)
Distant metastasis	
Lung	2 (15.4)
Bone	0 (0)
Liver	0 (0)
Brain	0 (0)

[a]Some patients had more than 1 recurrence site; [b]Recurrence at the cervix, uterus, upper 2/3 of the vagina, and parametrium; [c]The intrapelvic region includes the pelvic side wall and lower 1/3 of the vagina, does not include the pelvic lymph node

Discussion

Our study investigated LACC patients treated with CCRT. We found a late recurrence rate of 7.4% more than 3 years and of 2.2% more than 5 years after initial treatment. These rates are similar to those of other studies in LACC patients that have reported rates of recurrence at more than 5 years between 2.4% and 5.1% [20–22]. However, when compared with data on early-stage cancer from the same institute [19], the late recurrence rate at more than 5 years from our study is slightly smaller. Hanprasertpong et al. [19], who studied patients with cervical cancer stages IA2–IB1 and treated with radical hysterectomy, found a rate of recurrence of 4.8% more than 5 years after initial treatment. Because a locally advanced disease is known to be more aggressive than early disease, early recurrence is found more frequently in locally advanced cancers.

In our study, the patients with pretreatment anemia (hemoglobin level < 11 g/dL) at initial diagnosis experienced early tumor recurrence more frequently than late recurrence (using a cut-off point of more than 3 years). Several studies have shown that anemia correlates with tumor hypoxia [25, 26]. Moreover, we know that hypoxia is an important factor in tumor response to radiation therapy. Experimental studies have suggested that hypoxic cells are more resistant to radiation than normally oxygenated cells [27, 28]. In light of this information, we hypothesize that the anemic patients might have had residual microscopic disease after CCRT due to the effect of radioresistance, which might have led to early recurrence. Furthermore, a study that analyzed LACC treated with radiation therapy showed that patients with pretreatment hemoglobin levels of < 13 g/dL had a significantly lower median pO_2 level than those who had hemoglobin levels of ≥ 13 g/dL; this was associated with a significantly higher risk of treatment failure after 1 year [29]. In addition, we found that thrombocytosis (platelet counts ≥ 400000/μL) was more common in early recurrence. Patients who presented with pretreatment thrombocytosis may have micrometastasis at initial diagnosis and tend to develop early recurrence. There are many theories concerning the tumor-platelet interaction in solid tumors and the underlying mechanisms mainly associated with cytokines. Platelets can induce metastasis, i.e. activated platelets release cytokines to protect the circulating tumor cells from the host's immune system, as well as the proliferation and migration of tumor cells [30–32]. As mentioned above, anemia and thrombocytosis might be predictive characteristics of early recurrence. However, these differences were not detected when using 5 years as the cut-off point; this finding might have been due to the small population of patients with recurrence at more than 5 years. Further studies are needed to confirm our hypotheses.

When focusing on recurrence symptoms, even though we used the late recurrence cut-off point of more than 3 years and 5 years, more than 75% of patients in our cohort was symptomatic in both early and late recurrence. This result was concordant with those of other studies [19–21, 24]. In addition, we found that the lung was the most common distant metastasis site for late recurrence at more than 3 years; this corresponds to the reports of other late recurrence studies [19, 21]. Moreover, when analyzing patients who remained-tumor free for at least 5 years, the lung was observed to be the only site of distant recurrence. Referring to the "seed and soil" hypothesis, the lung (soil) might have a favorable microenvironment that is somehow specific for metastatic cervical cancer cells (seed); that is the reason why the lung is found to be the most common metastatic site for cervical cancer in any period of recurrence [33–35]. In light of our results, as a part of the surveillance plan, physicians should educate their patients to be able to recognize the early symptoms of recurrence and advise patients about the symptoms related to chest recurrence in any period of follow-up.

In our attempt to identify independent risk factors associated with late recurrence at more than 3 years, only stage III–IVA was found to be one. This result is consistent with those of a previous descriptive report by Sakurai et al. [22]; they studied LACC treated with radiation therapy and found that only stage III–IV was associated with late recurrence at more than 5 years. Currently, our report is the only study to have investigated independently factors associated with late recurrence in LACC patients who were treated with CCRT. Based on our results, we suggest

that patients with stage III–IVA and treated with CCRT should be considered to be at high risk of developing recurrence after more than 3 years. Hence, they should be subjected to longer follow-up compared with early-stage patients. Unfortunately, we did not find any factors significantly associated with late recurrence at more than 5 years. The number of patients in our cohort, who had late recurrence at more than 5 years, was low (n = 13). This might have affected the ability of our study to detect any associated factors. Further studies with larger sample sizes might be more useful in finding a potential association.

In our study, using 3 years as the cut-off point, SAR in the late recurrence group was significantly better than that of the early recurrence group. Sakurai et al. [22] reported that patients with early recurrence, within 2 years of the initial therapy, had a worse prognosis than those with recurrence after 2 years. Moreover, Kozaki et al. [9] reported that patients with a longer therapy-free interval had better survival. The therapy-free interval is also a good indicator for response to chemotherapy in patients with recurrent cervical cancer after CCRT. These findings can be explained by more indolent tumor biology associated with disease recurrence after 3 years compared with that recurring within 3 years. However, when using 5 years as the cut-off point, SAR between early and late recurrence was not significantly different. A possible explanation for this may be a small number of patients in the late recurrence group, which prevents the detection of any significant differences.

The main limitation of our study is its retrospective design. Moreover, we collected data from our database encompassing a long period (14 years). Inevitably, therefore, our patients received radiation via diverse treatment techniques, which have evolved over that period. The same is true about the investigation methods at initial diagnosis, as well as staging. Hence, it is reasonable to assume that these variations may have exerted some confounding effect on our results. Furthermore, according to the definition of vaginal cancer [36], the presence of a second primary vaginal cancer might have confounded our diagnosis of a local recurrence of cervical cancer if the disease occurred within 5 years after CCRT; therefore, the rate of local recurrence in our study may be overrated.

Conclusions

In conclusion, although the recurrence of cervical cancer is mostly observed during the first two years after initial treatment, in LACC patients after CCRT, late recurrence after 3 years is not rare. Even though we could not find a significant association between clinicopathologic factors and late recurrence after 5 years, 2.2% of our patients were found to experience late recurrence. We suggest that long-term follow-up should be considered, especially for the more advanced stages (stage III–IVA).

Conflict of interest

Authors declare no conflict of interest.

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